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THE PATHOLOGY OF NINETEEN CASES OF A PECULIAR AND SPECIFIC FORM OF NEPHRITIS ASSOCIATED WITH ACQUIRED SYPHILIS[1]

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The purpose of this paper is to direct attention to a peculiar and, as far as I have been able to determine, a hitherto undescribed form of nephritis which occurs not infrequently during the course of syphilitic infection.

For many years the observations of clinicians have led them to suspect the existence of a true syphilitic nephritis in adults. Pathological studies, however, have up to the present offered scant support for the belief that the spirochaete is able specifically to damage the kidney in a manner in any sense adequate to explain those cases of disturbed renal function occurring during the course of acquired syphilis in which, perhaps especially because of the beneficial effect of antisyphilitic therapy, the clinician has long suspected the etiological rôle of syphilis itself.

From the pathological standpoint we find Herxheimer (1), in his extensive review of the literature on the pathology of syphilis, devoting only a few words to syphilis of the kidney, stating that "on the whole, anatomically certain syphilis of the kidney is rare," and that while some cases in which there are round cell infiltrations and scars may be regarded as instances of syphilis of the kidney, "the only interstitial nephritis really characteristic (of syphilis) is that associated with gummata."

Aschoff (2) in his text-book of pathology, dismisses syphilitic nephritis in adults with a single sentence. "Multiple scars in the kidneys of syphilitic individuals," he writes, "have been regarded as the results of syphilitic inflammation by the process of exclusion."

[1] Presented before the Johns Hopkins Medical Research Society, February 12, 1932.

Kaufmann (3), likewise, in his text-book of pathology makes bare mention of syphilitic nephritis, referring only to star- or wedge-shaped atrophic areas containing hyalinized glomeruli and obliterated arteries, of which he disposes as a "wenig characteristische Veränderung."

MacCallum (4), even more tersely, confines himself to the remark that "changes leading to diffuse scarring and contraction of the kidneys due to syphilis have been said to occur."

Several years ago there came to autopsy in this Department a negro, 50 years of age, who died a few hours after having been admitted to the hospital in coma. The cause of death was found to be a cerebral haemorrhage, but there was also syphilitic aortitis and a remarkable type of destructive renal lesion which was completely unfamiliar. The character of the lesion suggested the possibility of a syphilitic etiology, but no description of such a lesion produced by the spirochaete (or, indeed, by any other agent) could be found, and no satisfactory opinion could be formed regarding either the significance of the lesion or its etiology.

After the lapse of about a year a second case at autopsy showed exactly the same extraordinary lesion, again associated with syphilitic aortitis. The suspicion of the possible relation of syphilis to the lesion became more strongly aroused. Soon a third case, precisely like the others, came under our observation, and then a fourth—each one in association with syphilitic aortitis. It seemed then that we might be dealing with a lesion of no great rarity, and one which might well be the result of syphilis or of the drugs used in the treatment of syphilis. It was decided, therefore, to search for the lesion in the microscopical sections of the kidneys from cases in our files showing definite acquired syphilitic lesions in other organs, for the frequency with which we were meeting the lesion since its recognition led us to suspect that we might have been overlooking it in the past in spite of its striking aspect, since it is a familiar fact that the eye all too commonly sees only that for which it has learned to look. The kidneys from 200 adult autopsies in which definite extra-renal lesions of acquired syphilis were present were therefore examined, and this unique form of nephritis was found in thirteen of the cases (6.5 per cent). As a control the kidneys from twice the number of adults (400) in which no syphilitic lesions were found in any organ at autopsy were examined. It would have been

entirely too time-consuming to have searched the clinical records for a history of syphilis in each of these cases in the effort to secure a definitely non-syphilitic group of controls, and besides, cases with negative history and negative Wassermann reaction are not necessarily non-syphilitic. It was recognized, therefore, that in the control group there would undoubtedly be cases which were syphilitic. For this reason twice the number of control cases were studied in order that even if 50 per cent of the fatal cases in this hospital were syphilitic (which is certainly too high a figure), there would still be a control group of non-syphilitics as large as the number of syphilitics studied. In the 400 control autopsies the renal lesion with which we are here concerned was found in two cases (Autopsies 10275 and 9577). When the clinical records of these cases were consulted it was found that one of the patients had a definite history of syphilitic infection and that both had a positive Wassermann reaction. In two other recent cases in which the lesion was found (Autopsies 12321 and 11604) there were, likewise, no other syphilitic lesions discovered at autopsy, but again the clinical records showed that both patients had strongly positive Wassermann reactions. A fifth similar case has just been brought to my attention by Dr. Kindell of this Department. Discussing the macroscopic peculiarities of the renal lesion with him brought to his mind a case which he had seen several years ago at Bay View, the City Hospital, in which the *gross* appearance of the kidneys had been puzzling, and which he remembered as having been similar to the lesion to be described here. Dr. Acton, the resident pathologist at Bay View, has kindly brought me the history and the sections of the kidneys of this case (B.V. 4231) and the characteristic lesion is beautifully shown. There were no syphilitic lesions found in other organs at autopsy but in this case again there was a definite history of syphilis and the patient had been receiving antisyphilitic treatment. Finally, another case has just come to autopsy (12324) in which the specific lesion is associated with a positive Wassermann reaction and syphilitic aortitis. In no instance in the large number of control cases studied has anything even resembling the lesion been encountered in a person who was not syphilitic.

Thus, in fourteen of the nineteen cases in which the renal lesion has been encountered there have been syphilitic lesions in other organs,

TABLE I

AUTOPSY NUMBER	YEAR OF DEATH	AGE	SEX	RACE	EVIDENCE OF SYPHILIS			EVIDENCE OF RENAL IMPAIRMENT		BLOOD PRESSURE	ASSOCIATED ORDINARY NEPHRITIS	ARTERIOLOSCLEROSIS	CONDITION OF PRESENT SPECIFIC LESION		ANTISYPHILITIC TREATMENT	CAUSE OF DEATH
					History	Extra-renal lesions	Wassermann reaction	Urine	Blood				Extent	Character		
6352	1920	38	M.	C.	+	Aortitis	0	Alb. +; W.B.C.; s.g. 1.025	Urea N. 30	170/50	None	0	++	Fresh	None	Aortic insufficiency. Cardiac failure
6760	1921	39	M.	C.	0	Aortitis; cutaneous syphilides	+	Alb. 4.5 gms./L.; W.B.C.; casts; "much débris;" phthalein 24 per cent; s.g. 1.012–15	N.P.N. 82	170/80	Very slight arteriolosclerotic nephritis	+	++++	Fresh, very advanced and scarred	Hg. several days before death	Aortic insufficiency Cardiac failure
7720	1923	31	F.	C.	0	Aortitis	+	Alb. ++; W.B.C.; casts; s.g. 1.018	N.P.N. 34	165/105	None	0	+	Fresh	Yes (type?) 5 yrs. before death	Fibrous myocarditis. Heart block. Cardiac failure
8438	1925	45	M.	C.	+	Syphilis of stomach	+	Alb. trace; W.B.C.; casts; s.g. 1.020		160/125	None	Slight	+	Fresh	None	Pyloric obstruction
8613	1925	56	M.	C.	0	Aortitis	+	Alb. 0; W.B.C.; s.g. 1.030			None	0	++	Fresh and advanced	None	Intestinal obstruction
9377	1926	26	F.	W.	0	Aortitis	0	Alb. +++; W.B.C.; casts; s.g. 1.008–16; phthalein 0	N.P.N. 91	150/100	Amyloid nephritis	0	++	Fresh and advanced	6 neo-diarsenol 3 yrs. before death	Uraemia
9544	1926	50	M.	C.	0	Aortitis	+	Died several hours after admission		240/135	None	+	++++	Most fresh, some advanced	None	Cerebral haemorrhage
9577	1926	27	F.	W.	0	0	+	Alb. +; W.B.C.; rare R.B.C.; phthalein, trace	Urea N. 95	108/64	Pyelonephritis	0	+++	Fresh and advanced	None	Stricture of ureter. Pyelonephritis
9951	1927	40	M.	C.	0	Aortitis; aneurysm	+	Alb. 0; W.B.C.; débris; s.g. 1.026; phthalein 60 per cent	N.P.N. 38	115/84	None	0	+	Fresh	Hg. several days before death	Asphyxia from aneurysm
10024	1927	37	M.	C.	+	Aortitis; aneurysm	+	Alb. ++; W.B.C. "lymphocytes;" casts; s.g. 1.026	N.P.N. 97	140/95	None	0	++++	Fresh	None	Aneurysm sinus of Valsalva. Cardiac failure

10275	1928	44	M.	C.	+	0	+	Alb. trace; W.B.C.; debris; s.g. 1.010–27; phthalein 50 per cent	N.P.N. 64	128/75	None	0	++	Few fresh, some advanced, most scarred	9 salvarsan 5 yrs. before death. Hg. arsenicals and bismuth shortly before death	Cancer of liver
10539	1928	43	F.	C.	0	Aortitis	+	Alb. +++; W.B.C.; casts; s.g. 1.020; phthalein 46 per cent		194/120	Very slight arteriolo-sclerotic nephritis	+	++	Fresh and advanced	None	Puerperal sepsis
11604	1930	33	F.	C.	0	0	+	Alb. 0; W.B.C.; s.g. 1.012		125/70	None	0	++	Fresh	None	Exophthalmic goitre. Postoperative death
BV 4231	1930	36	M.	C.	+	0	0*	Alb. ++; W.B.C.; s.g. 1.015–29	N.P N. 65	175/145	None	0	++++	Few fresh, most advanced and scarred	Yes. "All types, since 1918"	Myocardial insufficiency. Cerebral haemorrhage
11984	1931	30	M.	C.	0	Aortitis	+	Alb. 2.5 gms./L; W.B.C.; R.B.C.; casts; phthalein 23 per cent; s.g. 1.010	N.P.N. 140	240/136	Chronic arteriosclerotic nephritis	0	++	Advanced	None	Uraemia
12197	1931	35	F.	C.	0	Aortitis	+	Alb. ++++; W.B.C.; R.B.C.; s.g. 1.010; phthalein 10 per cent	N.P.N. 96	170/0	Chronic glomerulo-nephritis	0	+++	Some fresh, most advanced	6 salvarsan 2 yrs. ago. 9 bismuth 5 mos. before death	Chronic nephritis. Aortic insufficiency. Cardiac failure
12215	1931	35	M.	C.	+	Aortitis	+	Alb. +++; W.B.C.; R.B.C.; casts	N.P.N. 160	200/40	Chronic glomerulo-nephritis	0	+++	Advanced	None	Chronic nephritis. Aortic insufficiency Cardiac failure
12321	1931	27	F.	C.	+	0	+	Alb. ++; W.B.C.; s.g. 1.008–16	N.P.N. 26	100/70	None	0	+++	Advanced and scarred	3 arsphenamine and 1 bismuth 1 yr. ago	Tuberculous peritonitis
12324	1931	61	M.	C.	+	Aortitis	+	Alb. +; W.B.C.; casts; s.g. 1.015	N.P.N. 37	135/95	None	0	+	Some advanced, most scarred	6 salvarsan and 3 Hg. treatments 3 yrs. ago. 2 salvarsan 2 wks. before death	Malignant xanthoma of mediastinum. Cardiac failure

*Treated.

and in the remaining five cases there has been definite clinical proof of the existence of syphilis (positive Wassermann). This, together with other circumstances which will be discussed below, leads us to believe that the lesion represents a true and specific syphilitic nephritis in spite of the fact that spirochaetes have not yet been found in the routine Levaditi stains of the single case in which formalin-fixed material was available for study. The notorious inconstancy of the Levaditi method in the hands of most workers, and certainly in our own experience, robs this single negative result of any great weight. We shall, of course, continue the search for the spirochaete, with the various improved staining methods, in fresh cases as they appear; however, the unique character of the lesion and the sum of the evidence in favor of a syphilitic etiology lead us in the meantime to draw attention to this extraordinary form of nephritis in the hope that others also will attempt to decide definitely the question of its relation to syphilitic infection.

Description of the lesion. The characteristics of the lesion in each of the nineteen cases of this peculiar type of nephritis are so stereotyped that it will suffice to outline and to illustrate the general features of the process instead of describing each case separately. The clinical and pathological features of the various cases are summarized in Table I.

Macroscopically, in the less extensively affected cases one may see no appreciable change in the kidneys other than the presence of minute, glistening greyish-yellow flecks scattered here and there beneath the capsule and in the cortex. They have something of the appearance of grains of shining sand, and may project slightly above the surface of the organ. In cases showing more involvement the surfaces may still be smooth but the sharply defined, glistening flecks are present in striking profusion and may reach a diameter of several millimetres. On the cut surface these characteristic foci often appear as grey or greyish-yellow streaks containing shining flecks, replacing the striae and extending toward the medulla. In later stages of the process small and larger scars may roughen the surface of the kidney and distort the striae, and occasionally the characteristic, sand-like, glistening flecks can be seen in and about the scars.

Microscopically, the lesion is found to consist in dense, focal accumulations of mononuclear cells situated in the interstitial tissue, es-

pecially in the cortex. They may be just beneath the capsule or in the deeper layers, and the larger foci extend from the surface well down to the medulla. There are also distinctly perivascular mononuclear accumulations about the vessels in the kidney and even in the capsule and pericapsular tissue. The cells are chiefly small lymphocytes, but large lymphocytes, macrophages and plasma cells are also present, and in some cases a few eosinophiles. These dense mono-

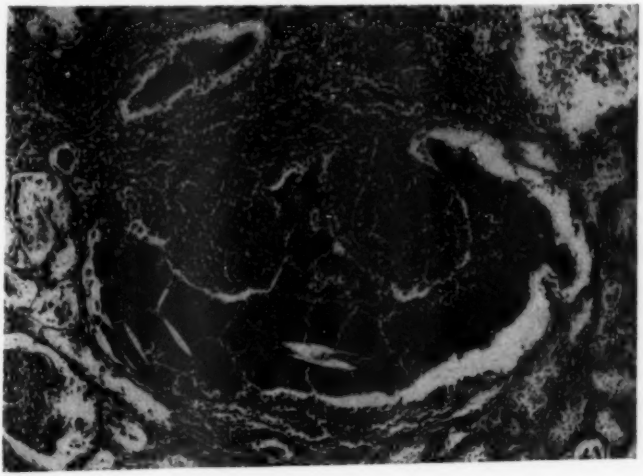

FIG. 1. TWO SPHERICAL NODULES OF INFLAMMATORY CELLS HERNIATING INTO A DILATED TUBULE CONTAINING AMORPHOUS DÉBRIS OF DISINTEGRATED EXUDATE

In the débris can be seen cigar-shaped clefts from which cholesterine crystals have been dissolved out during the process of embedding.

nuclear cell accumulations which extend irregularly through the interstitial tissue and compress and replace many tubules, have the curious tendency to be gathered into sharply-outlined spherical nodules which encroach upon the tubules, and by projecting into them in the most extraordinary manner often narrow the lumen markedly. These spherical nodules of inflammatory cells projecting into the tubules constitute one of the striking and unique characteristics of the

lesion (figs. 1, 2, 3). By following this process at different stages it appears to begin as a localized involvement of the wall of a convoluted tubule adjacent to an area of interstitial inflammation. Special stains show that the basement membrane beneath a few cells first becomes destroyed, and the epithelial cells overlying this stretch

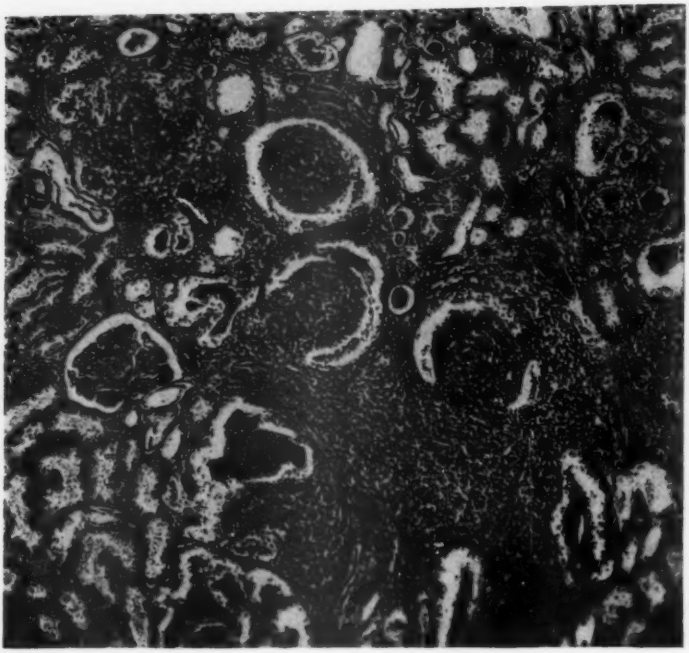

FIG. 2. INTERSTITIAL INFLAMMATORY INFILTRATION AND SEVERAL SPHERICAL NODULES OF CELLS PROJECTING INTO DILATED TUBULES

One such nodule has been cut across in a plane which does not include its attachment to the side of the tubule, and it appears as a round mass of cells lying free in the tubule. A crystal of cholesterine is seen in the lower right corner.

of the tubule become greatly swollen and the cytoplasm stains poorly. The epithelium then becomes pushed inward more and more by the extension of the inflammatory cells from the interstitial tissue (Fig. 4), until the projecting mass, accompanied by sprouting connective tissue

cells and capillaries, finally lies well within the tubule usually in the form of a perfect sphere attached by a broad or narrow base, depending upon the extent of primary destruction of basement membrane through which the inflammatory mass literally herniates. At this

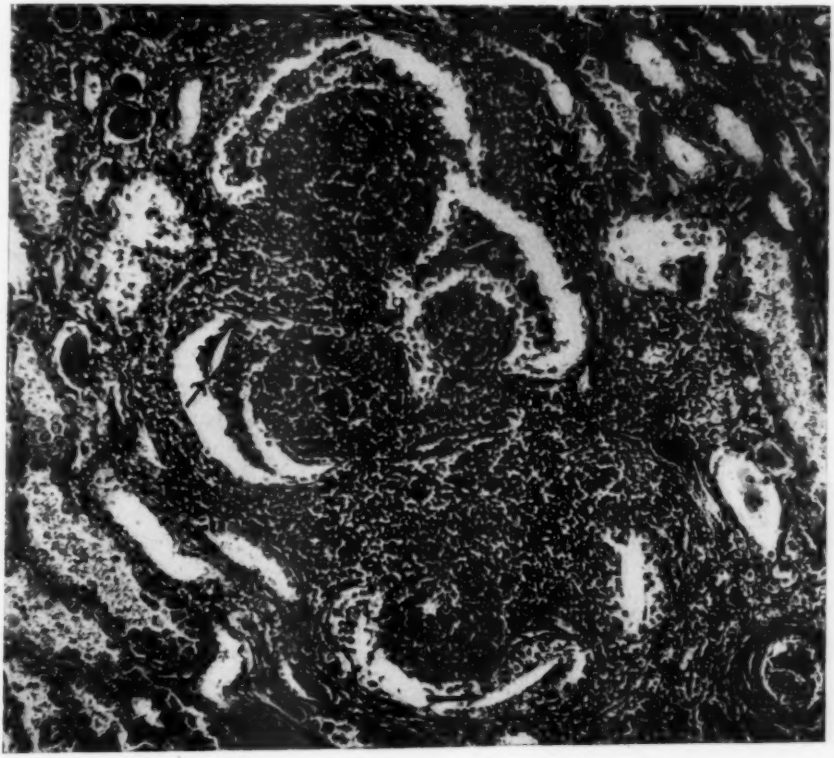

FIG. 3. HIGHER POWER OF SEVERAL SPHEROIDAL NODULES HERNIATING INTO TUBULES

The arrows point to cholesterine crystals

stage the epithelium, which proliferates to cover it completely, has become almost cuboidal and the cells are frequently vacuolated. This process occurs particularly in the walls of tubules which have

become dilated because of obstruction below caused by the interstitial inflammation, so that the projecting nodules commonly have the opportunity of reaching a size equal to that of a glomerulus.

The second peculiar characteristic of this form of nephritis is the presence of crystals in the lumen of the affected tubules adjacent to the areas of interstitial inflammation. In the early stages the lumen contains large, fat-laden macrophages, occasional desquamated epithelial cells and polymorphonuclear neutrophils with, in some

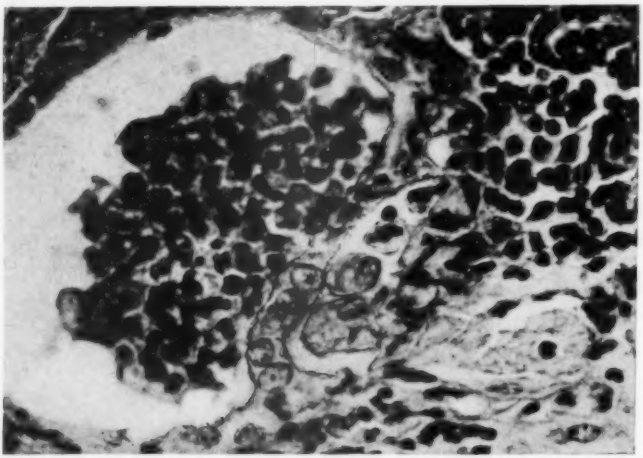

FIG. 4. EARLY INVOLVEMENT OF A TUBULE. EXUDATE IN THE LUMEN

The epithelial lining (outlined with ink for the purpose of clarity) is pushed inward toward the lumen by invasion of wandering cells from the inflamed interstitial tissue. The basement membrane is destroyed at this point, and several large macrophages can be seen immediately beneath the epithelium.

cases a scattering of eosinophils (Fig. 5). The tubular contents undergo degeneration and become converted into a granular, amorphous mass of detritus, staining purplish with haematoxylin, from which, at length, even the nuclear fragments disappear. As this occurs, and indeed sometimes while there are still well preserved inflammatory cells in the lumen, there appear numerous crystals of varying size, and it is these undoubtedly which give the glistening

appearance to the foci seen on macroscopic examination. In paraffin sections one sees only pointed clefts in the cellular débris in the tubule (Figs. 1, 3), for the crystals are dissolved out during the process of

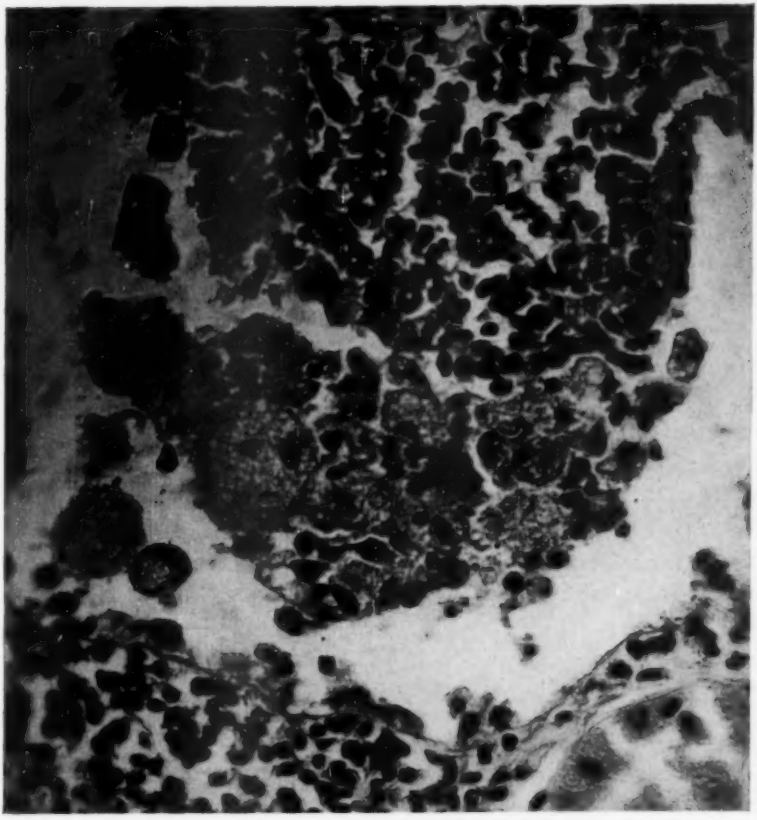

FIG. 5. A STAGE A LITTLE LATER THAN FIGURE 4

There is beginning herniation of inflammatory cells into the tubule, and the large, lipoid-laden macrophages can be well seen in the lumen.

embedding and staining, but in thick frozen sections they are clearly visible and can be seen, on teasing favorable sections, to have the

shapes and "broken corners" characteristic of cholesterine crystals. Their abundance in a recent autopsy performed by Dr. Brawner has permitted us to determine that they have the solubility properties and give sharply the microchemical color reactions characteristic of cholesterine. In some instances the crystals are surrounded by foreign body giant cells.

That much of the cellular debris and crystalline cholesterine remains long in the tubules instead of passing out promptly in the urine, is explained partly by the narrowing of the lumen by the encroaching spherical masses of inflammatory cells, and also by the fact that many tubules are focally destroyed and replaced at one level by the inflammatory process, with the result that material within the dilated lumen at a point higher up cannot escape past the obliterated portion of the tubule.

The extent of the process varies greatly in different cases. It is always a focal lesion and there may be only one or two such areas in an entire microscopic section, but in several cases both kidneys are so diffusely affected that one low-power field after another is severely involved in the process and the loss of parenchyma is very great indeed (Figs. 6, 7). Many tubules are obliterated and replaced by the dense mononuclear infiltrations, their associated glomeruli atrophy and become converted into hyaline scars, and the amount of functioning renal tissue becomes greatly reduced. Although the spherical masses of mononuclear cells suggest at first glance glomeruli infiltrated with inflammatory cells, careful study of various stages shows that they are certainly not, but that they are formed rather by the invasion of the walls of tubules, as described above. Glomeruli may, indeed, be caught in the area of inflammation and destroyed, and many may become obliterated following the destruction of their dependent tubules, but the process attacks primarily the interstitial tissue and the tubules rather than the glomeruli. The photographs illustrate the condition, which is so unique, so stereotyped and so different from all other renal lesions that, once seen, if encountered again it could hardly be overlooked or confused with anything else.

With the passing of time the mononuclear cells become replaced by scars in which the remains of tubules and glomeruli are found. One can see all stages of this process in different cases and sometimes in

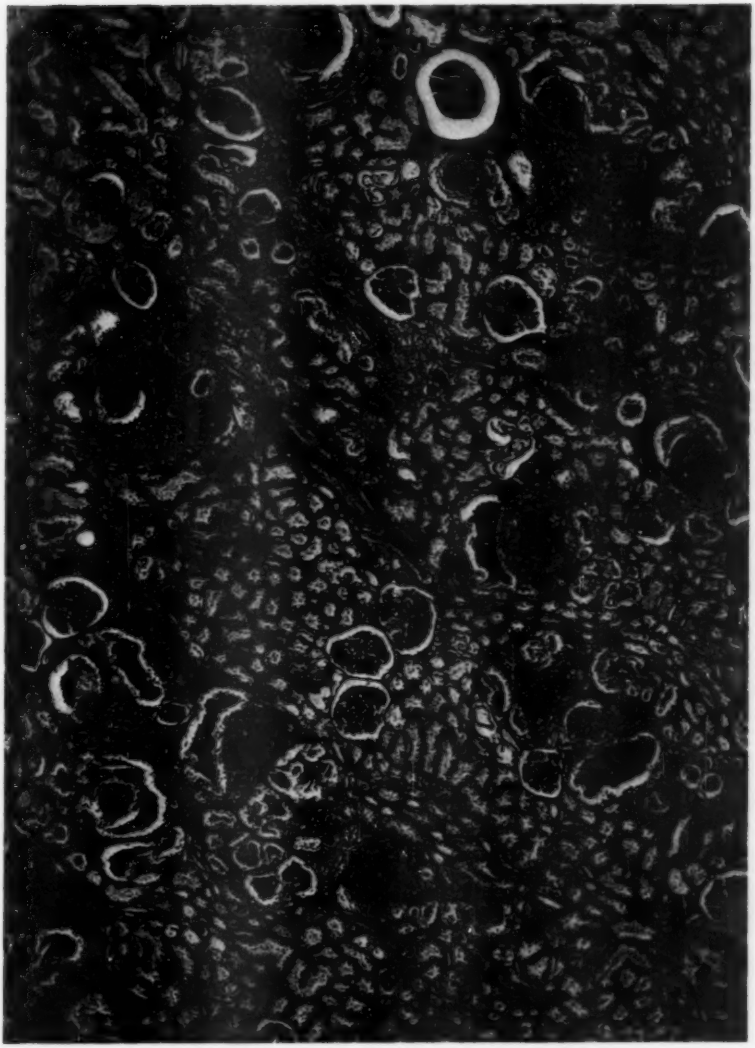

FIG. 6. A LARGE FIELD UNDER LOW POWER TO SHOW THE EXTENT OF THE PROCESS

This is case 9544, in which, aside from the present form of lesion, no ordinary nephritis was present.

the same case. Even the exudate within the tubules may undergo organization, connective tissue cells sprouting into the lumen from the inflamed interstitial tissue where tubules have lost their epithelial cells. The extension of connective tissue into the lumen seems to be the result

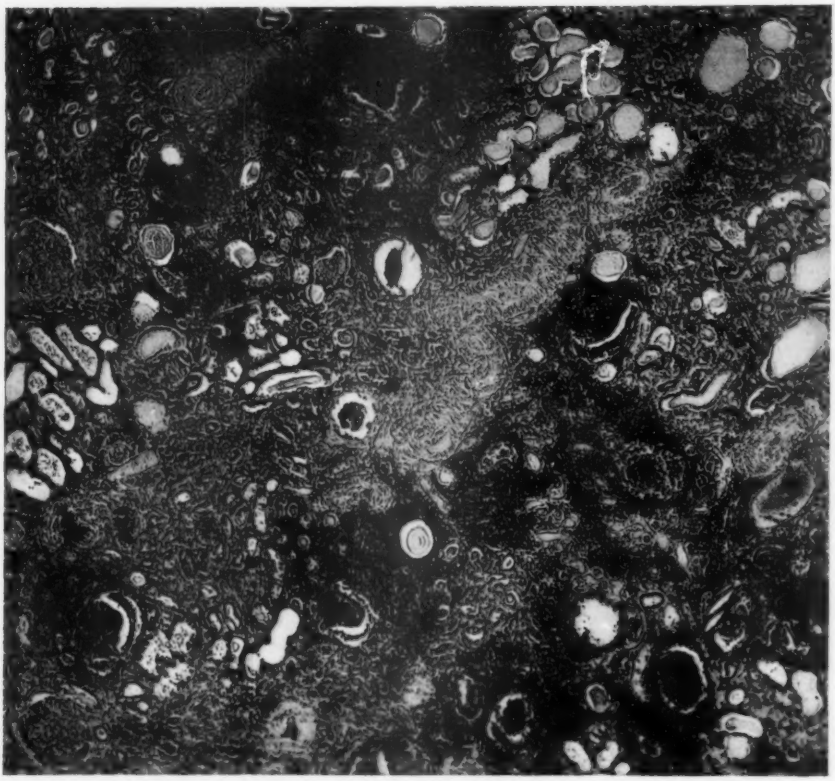

FIG. 7. A LARGE FIELD UNDER LOW POWER TO SHOW THE EXTENT OF THE PROCESS IN CASE 12197 IN WHICH THE PRESENT LESION OCCURRED IN A KIDNEY WHICH WAS ALSO THE SITE OF AN ORDINARY GLOMERULONEPHRITIS

The dark areas represent the interstitial inflammation of the present lesion. The spheroidal herniations can be seen, and crystals of cholesterine are clear in the lower right corner.

of the above described localized destruction of the basal membrane which in ordinary forms of nephritis remains intact and serves as a limiting barrier against any interstitial inflammation. Certainly it is through these gaps in the basement membrane that the inflammatory, connective tissue cells and even capillaries push into the tubule. The connective tissue so formed may obliterate the lumen, and when crystals of cholesterine lie in exudate which undergoes organization they become surrounded by foreign body giant cells, and in the end one sees in such areas the crystals with giant cells about them, lying in a matrix of scar tissue rich in inflammatory cells. The end result in the more extensive cases is a kidney with many focal cortical scars, often containing abundant lymphocytes. In some cases the scars may be quite large and wedge-shaped. One case shows beautifully that extensive scars can actually result from this specific process, for a large wedge-shaped area of tissue which was contracted and depressed beneath the surface was found microscopically to be a scar containing many hyalinized glomeruli and collapsed tubules, but also here and there dilated tubules; and this scar is sharply marked off from the surrounding tissue by reason of its being densely infiltrated with mononuclear cells which bulge in the characteristic spherical fashion into the few dilated tubules which remain, and many cholesterine crystals are still seen imprisoned in those tubules (Figs. 8, 9). Eventually, however, all characteristics of the present process disappear and there remains either a totally non-specific scar or, more commonly, a scar unusually rich in lymphocytes, and frequently containing a group of small, atrophic tubules lined with flattened-out epithelium and often containing hyaline casts. These altered tubules, grouped together in a scar, remind one of small, colloid-containing thyroid acini. It is perfectly clear from the study of our material that multiple, nondescript, circumscribed scars may result from the process here described, and I have encountered many cases in syphilitics in which the presence of such scars, often rich in lymphocytes, in kidneys still showing perivascular round cell infiltration about the vessels of the medulla and pelvis, seem almost surely to represent the end stage of the inflammatory and destructive process here described. However, the present series of nineteen cases includes only instances in which the characteristic spheroidal bulging into the tubules and the presence of crystals of cholesterine are clearly evident.

The stage of syphilitic infection in which the present lesion appears. While it is true that all of the present cases have been found in patients in the tertiary stage it must be stated that instances of secondary

FIG. 8. VERY LOW POWER MAGNIFICATION OF A LARGE SECTION SHOWING A LARGE, WEDGE-SHAPED SCAR PRODUCED BY THE PRESENT PROCESS. SEE FIGURE 9

syphilis are rare in our files. In the present series of 200 syphilitics there were only two autopsies on patients in the secondary stage.

It should also be stated in regard to the frequency of the association of the lesion with syphilitic aortitis (12 out of the 17 cases) that aortitis is by far the most common internal syphilitic lesion in our files (175 of the 200 syphilitic cases studied). That the presence of the renal lesion is not necessarily dependent upon the existence of manifest lesions in other organs is shown by the five cases in which no other lesion was found but in which there was a history of infection and a positive Wassermann reaction. The great preponderance of negroes

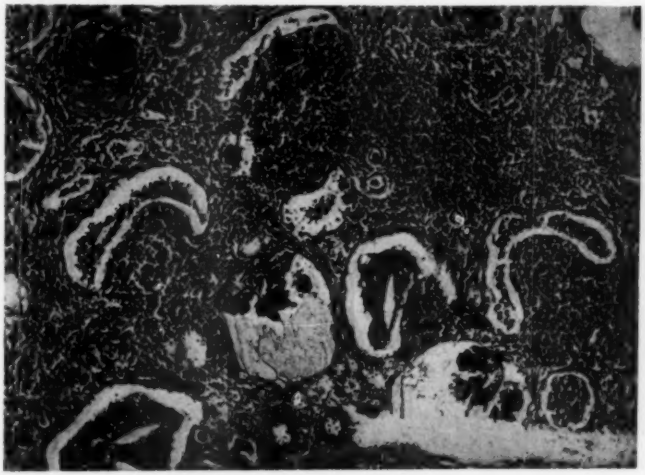

FIG. 9. HIGHER MAGNIFICATION CHARACTERISTIC OF ANY PORTION OF THE SCAR SHOWN IN FIGURE 8

The herniating, spheroidal nodules and the crystals of cholesterine are evident

in the present series can be accounted for to some degree at least by the relative preponderance of negroes over whites in the syphilitic material in this Department. Roughly, three-fourths of the 200 syphilitic cases examined were in negroes.

Circumstances supporting the syphilitic etiology of the lesions. Up to the present spirochaetes have not been demonstrated in the lesion and it is, of course, absolutely necessary to find them there in order to be perfectly sure that the process is a syphilitic one. However,

while awaiting the opportunity for the application of special staining methods, which fresh cases will provide, the evidence in favor of the syphilitic etiology of this form of nephritis may be summarized.

First, in every instance in which the lesion has been found it occurred in a syphilitic individual. It was found in the files of this Department in 13 (6.5 per cent) of 200 consecutive autopsies on patients with syphilitic lesions in tissues other than the kidneys.

Second, in five instances the lesion has been encountered in the absence of any discovered syphilitic lesions in other organs. In each of these cases, however, reference to the medical history revealed a definite story of syphilis, all five patients having been known to have had positive Wassermann reactions.

Third, in only two of 400 routine autopsies on patients without evidence of syphilis at autopsy was the lesion encountered, and reference to the medical history showed that each of these individuals had a strongly positive Wassermann reaction. These *400* control cases were patients of the same racial distribution, between the same age limits and who came to autopsy during the same period of time as the *200* syphilitic cases of which 6.5 per cent showed the lesion.

Fourth, that the lesion is not the result of antisyphilitic treatment is clear from the fact that it occurs in florid form in cases in which it was definitely ascertained that the patient had received no form of antisyphilitic treatment at any time. As a matter of fact, Table I shows that only nine of the nineteen cases had received treatment. Furthermore, neither mercury, bismuth, arsenicals, nor indeed any other drug as far as is known, is capable of producing anything resembling this lesion.

Fifth, the type of reaction is that entirely characteristic of syphilis—mononuclear cell accumulations with the familiar perivascular round-cell infiltrations so regularly seen in syphilitic lesions. In regard to the several cases in which a scattering of eosinophils were found, it may be remarked that eosinophils have long been known to occur in numbers in syphilitic lesions, especially in the tertiary stage in which all of the present cases fell (5). As for the presence of the crystals of cholesterine, these, too, are encountered in syphilitic lesions. Figure 10 shows the presence of such crystals in the media of the aorta in the lesion of syphilitic aortitis, and Figure 11 shows them in abundance in a tertiary testicular lesion.

FIG. 10. CRYSTALS OF CHOLESTERINE IN A SYPHILITIC LESION IN THE MEDIA OF THE AORTA

The hyalinized, thickened intima can be seen at the upper part of the photograph

FIG. 11. CRYSTALS OF CHOLESTERINE IN THE SYPHILITIC GRANULATION TISSUE AT THE MARGIN OF THE CASEOUS PART OF A GUMMA OF THE TESTIS

The caseous part of the gumma lies toward the right

Sixth, that spirochaetes pass from the kidney into the urine in syphilitic individuals has been well established by numerous investigators (6). It is of particular interest in this connection that Warthin (7), by means of his special stain, was able to follow the passage of spirochaetes from the interstitial tissue through the wall of the tubule into the lumen in the kidneys of two syphilitic adults which he studied. He was convinced, and pictures convincingly, that the primary attack of the spirochaete is upon the interstitial tissue, that the invasion of the tubule is secondary and that the glomeruli are not primarily damaged. This fits the present observations very well indeed, for it was perfectly clear to us before reading Warthin's paper that the earliest and most affected part of the kidney is the interstitial tissue, and the localized disintegration of the basement membrane which, as we have seen, initiates the involvement of the tubule, could well represent the result of the beginning of the penetration of the spirochaete into the tubule as observed by Warthin. Warthin was particularly concerned with the relation of the spirochaetes to the parenchyma rather than with the minute histology of the lesion in the kidneys which he studied, and his brief description contains no mention of the curious invasion of the tubules by the spherical masses of round cells, or of the presence of crystals of cholesterine in the detritus-laden tubules, which have been pointed out as characteristic features of the present cases; but he does say that, in his cases in which the spirochaetes were demonstrated, the interstitial tissue showed "an increase in the number of small cells, the majority of these being of the lymphocyte or plasma cell type," and that the tubules contained "a granular detritus from exudate or broken down cells." It is not impossible that he may have been staining spirochaetes in the lesion here described, for Warthin's microscopical description is exactly that which is commonly found in our own protocols of the cases here described.[2]

[2] Since this was written Dr. Carl V. Weller has kindly sent me some embedded tissue from one of the cases studied by the late Dr. Warthin. Sections of this material did not show the characteristic lesion described in this paper, but it may be stated that neither Dr. Weller nor myself could find spirochaetes in this particular portion of the kidney. Whether the specific lesion existed in other parts of the organ, or whether this case represents an early stage of the process before the formation of the spheroidal nodules and cholesterine crystals is not certain.

In the light of the evidence that the spirochaetes commonly pass through the kidneys into the urine, that their passage from the interstitial tissue into the tubule has been demonstrated; that the present lesion begins in the interstitial tissue and extends to involve the tubule, that the lesion has the essential characteristics of syphilitic lesions in other organs, that it has been found only in syphilitics, and has not occurred in the large number of non-syphilitics studied, and that it is not a result of antisyphilitic treatment, it seems that in all reasonable probability it represents a true syphilitic nephritis. However, there is no form of evidence which can be regarded as sufficient to replace the necessity of demonstrating spirochaetes in the lesion in order to establish the syphilitic etiology, and until this is accomplished the evidence, strong as it may be, must be regarded as incomplete.

The relation of the lesion to clinical nephritis. It was stated in the beginning of this paper that many clinicians over a long period of time have expressed the belief that syphilis plays an etiological rôle in nephritis, which condition, they have believed, occurs with more than ordinary frequency during the course of syphilitic infection. It is therefore pertinent to enquire whether the specific lesion here described can be related in any way to this old clinical belief.

In the first place, it must be pointed out that renal insufficiency can be expected to result from this type of lesion only when it is very widespread, for it is primarily an interstitial nephritis, and it is well known that the ordinary form of interstitial nephritis, such as that associated with diphtheria for example, (which, it may be remarked, never possesses the specific and peculiar characteristics of the present lesion) causes no appreciable symptoms unless the involvement of the kidneys is very extensive. That the destruction of parenchyma caused by the present lesion can be extensive is clearly evident from several cases in this series (Nos. 6760, 10024, B.V. 4231 and 9544). Unfortunately, however, one of these cases was complicated by a superimposed ordinary nephritis of slight degree, two others by cardiac failure, and the fourth died within a few hours after admission before a proper study could be made. While it is thoroughly well known that chronic passive congestion of the kidneys resulting from cardiac decompensation may lead to a lowering of the renal function,

it is, nevertheless, of interest that in both of the cases in which the present lesion was extensive, but complicated by myocardial insufficiency, the clinical study led to a diagnosis of chronic nephritis in addition to cardiac decompensation.

The presence of the above complicating factors in the cases of the present series with widespread lesions renders them inadequate to permit one to form any proper conclusion as to the clinical signs and symptoms which extensive and uncomplicated involvement of the kidneys by this specific process may be expected to produce. It must remain for the future study of uncomplicated cases to establish the clinical aspects of this condition in its florid form. The contents of the tubules indicate that a careful study of the urine will show the presence of large numbers of mononuclear cells, many containing doubly refractile lipoid, in addition to polymorphonuclear leucocytes, of which a considerable number may be eosinophiles. The presence of the lipoid-laden phagocytes may, indeed, serve as an aid in the diagnosis of the condition. It is of particular interest that the clinical examination of the urine in one of the present cases uncomplicated by ordinary nephritis disclosed the presence of "white blood cells, *predominantly lymphocytes*." Whether the crystals of cholesterine themselves escape into the urine, or whether they are formed from the cholesterine esters of degenerating lipoid-holding macrophages only in tubules which are permanently obstructed, must be decided by a more careful study of the urinary sediment than was carried out on any of the present cases.

It may be remarked that much has been written by Munk (8) and others of the association of syphilis with lipoid nephrosis. Since the presence of cholesterine is such a prominent feature of the lesion here described, one has at least to consider the possibility that this lesion may represent the residue of a previous lipoid nephrosis, the cholesterine esters having become converted into crystals of cholesterine. There is nothing, however, which really substantiates such a view. In the first place, the past histories of these patients fail to disclose any previous illness suggestive of nephrosis. In the second place, the autopsies which have been performed on cases of lipoid nephrosis of supposedly syphilitic etiology have shown only the ordinary features of nephrosis with no interstitial inflammation whatever, and autopsies

on cases of lipoid nephrosis performed years after the onset, have never, in our own or in others' experience, shown anything faintly suggesting the present lesion. Finally, in the cases here reported the lesion is seen to represent not an inactive residue of a former, different condition, but rather a process which is itself an independent, active and progressive one. All stages of involvement of the interstitial tissue and tubules can be seen, and in many of the tubules the exudate is perfectly fresh, consisting of well preserved mononuclear and polymorphonuclear cells.

Since pathology has heretofore offered no support for the existence of a true syphilitic nephritis, it has been the practice in many clinics to avoid antisyphilitic treatment in the case of nephritics who have syphilis, because of the possibility that the drugs might injure the kidney. However, there have been many reports of the favorable influence of antisyphilitic treatment on cases of nephritis developing during active syphilitic infection and it has been urged, in the belief that nephritis may be caused by the spirochaete, that arsenical antisyphilitic therapy should not be withheld in such cases. Certainly, if the present form of nephritis is actually the result of syphilitic infection of the kidney, as it so strongly appears to be, antisyphilitic therapy should be of distinct value in stopping the progress of the disease. Marked evidences of the healing of the lesions are present in well-treated cases in the present series, especially in B.V. 4231, but it must be stated that other cases show that, as is true of any tertiary lesion, the gradual replacement of the foci by scars may proceed even in the absence of treatment. It is perfectly obvious that when the present lesion makes its appearance in a kidney which is the site of an ordinary nephritis as in cases 6760, 10539, 11984, 12197, and 12215, the additional widespread destruction of tissue by this process can be a matter of very serious moment indeed, for the reserve parenchyma in such cases falls under the attack of two separate and independently progressive destructive processes, and the onset of renal failure will unquestionably be hastened (Fig. 7). From what is known of the effects of arsenical therapy upon the kidney it is safe to say that in the vast majority of the cases the damage produced by the drug itself is negligible in comparison with the damage which can be caused by the process described in this paper. From a theoretical standpoint

one has of course to consider the possibility that the rare occurrence of a Herxheimer reaction in a kidney which is also the site of an ordinary nephritis might be even more dangerous than the lesion described in this paper. I have searched the clinical records of the treated cases in the present series and there is nothing in any of them which suggests in any way that treatment was followed by a flare-up of the renal process.[3] However, it is necessary to await further correlated clinical and pathological studies on well treated cases of ordinary nephritis complicated by this lesion in order to form a proper judgment of the effect of treatment. At present there are enough clinical reports of the beneficial effect of antisyphilitic therapy on cases of nephritis in syphilitics to warrant the administration of treatment during nephritis, and the frequency with which the present lesion occurs in syphilitics lends strength to the view of those who urge the prompt treatment of syphilis *especially* when nephritis is present. The cure of the lesion described here and the prevention of its further spread should obviously be of great service in prolonging the life of any nephritic whose kidneys are subjected to this additional damaging process, and to whom the preservation of every particle of healthy renal parenchyma is a matter of the utmost importance.

The few autopsies which have been reported on cases of clinical nephritis of supposedly syphilitic etiology have heretofore disclosed only a non-specific, ordinary glomerulonephritis, differing in no way from the banal form encountered in non-syphilitics. In the light of the evidence concerning the relation of foci of infection, (especially in the nasopharynx and sinuses) to nephritis, which the recent careful studies of Longcope (9) have greatly strengthened, it may not be amiss to suggest that some cases of nephritis of non-specific pathological character which occur in syphilitics, especially during the secondary stage, may possibly be related to secondary bacterial infection of the ulcerated mucous membranes rather than to the spirochaete itself. From this standpoint any increased tendency to the occurrence of nephritis in acquired syphilitics would be comparable to the cir-

[3] Dr. Alan M. Chesney informs me that his records show that symptoms warranting the diagnosis of an Herxheimer reaction in any region of the body have been very rare occurrences as a result of the thousands of antisyphilitic treatments administered in this Hospital during the last twenty years.

cumstance obtaining in congenital syphilis. It is well recognized that infants with congenital syphilis are distinctly more susceptible to nephritis than are non-syphilitic infants, and much has been written on the subject of "congenital syphilitic nephritis." In a series of cases which I have recently studied in which there was well-marked clinical nephritis in infants (from one to fourteen months of age) with congenital syphilis, the lesion in every case except one was merely a stereotyped, ordinary glomerulonephritis, sometimes, indeed, superimposed upon the characteristic, perivascular myeloid-cell infiltrations which stamp the kidney of the congenitally syphilitic, but sometimes present in the complete absence of any characteristic syphilitic alteration in the kidney including the retardation of development common in congenital syphilis. The study of these cases made it seem very probable that the glomerulonephritis was related not to the syphilitic infection, but rather to the secondary bacterial infection of the nasopharynx ("snuffles"), and that the increased susceptibility of syphilitic infants to glomerulonephritis might be merely an expression of the increased frequency of foci of bacterial infection resulting from syphilitic destruction of nasal mucous membranes. The reported beneficial effects of antisyphilitic treatment on cases of glomerulonephritis in both congenital and acquired syphilis would be explainable on this basis by the clearing up of the syphilitic ulcerations which provide a ground for the secondary infection. There was, however, one instance in the series of cases of clinical nephritis in congenitally syphilitic infants in which the damage done by the spirochaete itself to the interstitial tissue and to the parenchyma of the kidneys was so widespread that most of the substance was destroyed and replaced by foci of necrosis, fresh scars and cellular infiltrations characteristic of congenital syphilis of the kidney, and clinical renal insufficiency appeared in the absence of any of the lesions characteristic of ordinary glomerulonephritis. The present studies indicate, therefore, that whatever may be the relation of the spirochaete to the ordinary forms of glomerular and tubular nephritis, occurring during syphilitic infections, in both congenital and acquired syphilis the spirochaete itself can specifically cause the destruction of enough of the functioning parenchyma to bring about renal insufficiency, even though the specific damage in congenital syphilis

(foci of necrosis with scarring) and in acquired syphilis (the lesion here described) is in most cases not extensive enough to reduce the amount of functioning tissue to the point of insufficiency.

SUMMARY

A peculiar and hitherto unrecognized, but not uncommon form of nephritis associated with acquired syphilis is described. It has been found in 6.5 per cent of 200 autopsies in which there were definite syphilitic lesions in other organs, and in five additional cases in which no other syphilitic lesions were found at autopsy but in which there was definite clinical proof of the existence of syphilis (positive Wassermann reaction). Although diligently searched for in four hundred control autopsies, in no instance has the lesion been found in the absence of syphilis.

The evidence that the lesion represents a true syphilitic nephritis is presented, and the relation of the process to clinical nephritis occurring during the course of syphilitic infection is discussed.

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HYPERTHYROIDISM AND DIABETES MELLITUS

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Of 200 patients operated upon in the Surgical Service of the Johns Hopkins Hospital during the winter of 1929 twenty (10 per cent of the total) had diabetes mellitus. Among the last 200 patients suffering from hyperthyroidism admitted to the Medical Service fifty-four (27 per cent) showed glycosuria; of these, three (1.5 per cent of the total) were considered to have diabetes mellitus. Among the last 400 cases of diabetes mellitus treated upon the same service five (1.2 per cent) were complicated by hyperthyroidism. These figures agree closely with those of Joslin and Lahey (15) from a much larger series of cases, and indicate that the coincidence of hyperthyroidism and diabetes mellitus is no greater than the incidence of the latter in an unselected group of surgical patients.

The accompanying charts contrast the carbohydrate metabolism of four patients. Chart I contrasts the *glucose* intake and output over a period of 26 days in the case of W. A., a young man of 22 years who suffered from severe diabetes and was treated in the Johns Hopkins Hospital before the discovery of insulin, with corresponding data in the case of G. L. B., a girl of approximately the same age as W. A., who suffered from severe hyperthyroidism. In the first instance (W. A.) the carbohydrate tolerance was extremely low; in the second (G. L. B.) the patient consumed 500 gm. of carbohydrate daily without glycosuria. Charts II and III outline graphically the clinical course of two cases in which hyperthyroidism and diabetes coexisted. Abstracts of the clinical records of these cases follow.

Case I. M. E. (Unit no. 33482) a married white woman, aged 29, was admitted Oct. 7, 1930, complaining of goiter and diabetes. Her sister, at that time aged 36, had undergone an operation for goiter 16 years previously. The patient herself had been aware of a lump in the right side of the neck since childhood but had never had symptoms of hyperthyroidism before 1927.

Present illness: Five years prior to admission the patient noted first increase

of appetite and thirst, loss of weight, and polyuria. She consulted her physician who found a glycosuria and advised limitation of carbohydrate in her diet.

Following the birth of her daughter in 1927 the patient noticed that the mass in her neck was increasing in size and that she was more nervous and irritable. Within the next year she noted tremor of the hands, tachycardia, palpitation and greatly increased susceptibility to fatigue. In the spring of 1929 she entered another hospital where she received medical treatment including insulin and iodine. In spite of this, the glycosuria persisted, and thyroidectomy was not attempted. She remained in the hospital for five weeks and was discharged only slightly improved. During the twelve months prior to admission to Johns Hopkins Hospital polyphagia, polydypsia and polyuria increased progressively, and

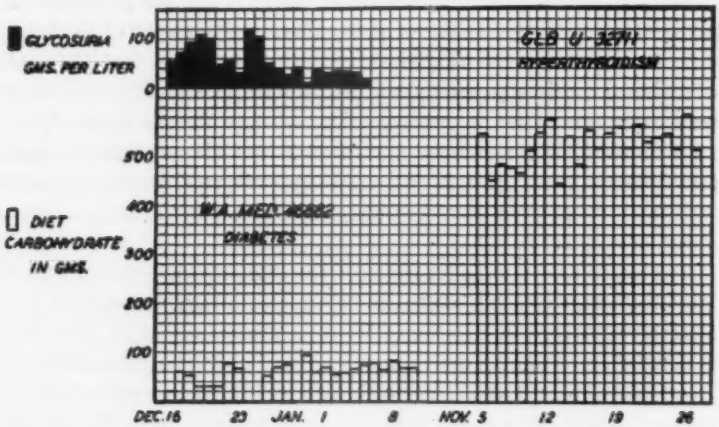

CHART I. CONTRASTING THE CARBOHYDRATE TOLERANCE OF A CASE IN DIABETES MELLITUS WITH THAT IN A CASE OF HYPERTHYROIDISM

the patient lost 60 pounds in weight. Drenching sweats occurred frequently during the six months before her entry and for the last two months she had suffered from dyspnoea on moderate exertion.

Physical examination: Temperature 99.2° F., Pulse 120, Respirations 24. A restless woman, somewhat under weight. The skin was warm; there was profuse perspiration over the entire body. The palms and soles were wet. Beads of sweat were present over the entire left side of the face; the right half of the face and neck was dry. Fine tremor of extended hands and fingers. No exophthalmos. Right lid-slit slightly narrower than left. Right pupil slightly smaller than left; both reacted to light. Fundi normal. A nodular mass occupied the position of the thyroid, chiefly involving the right lobe. There were no thrills

or bruits over it. The heart was not enlarged; the heart sounds were loud and forceful; there was a blowing systolic murmur in the pulmonic area. B. P. 132/82. Lungs clear. Spleen palpable.

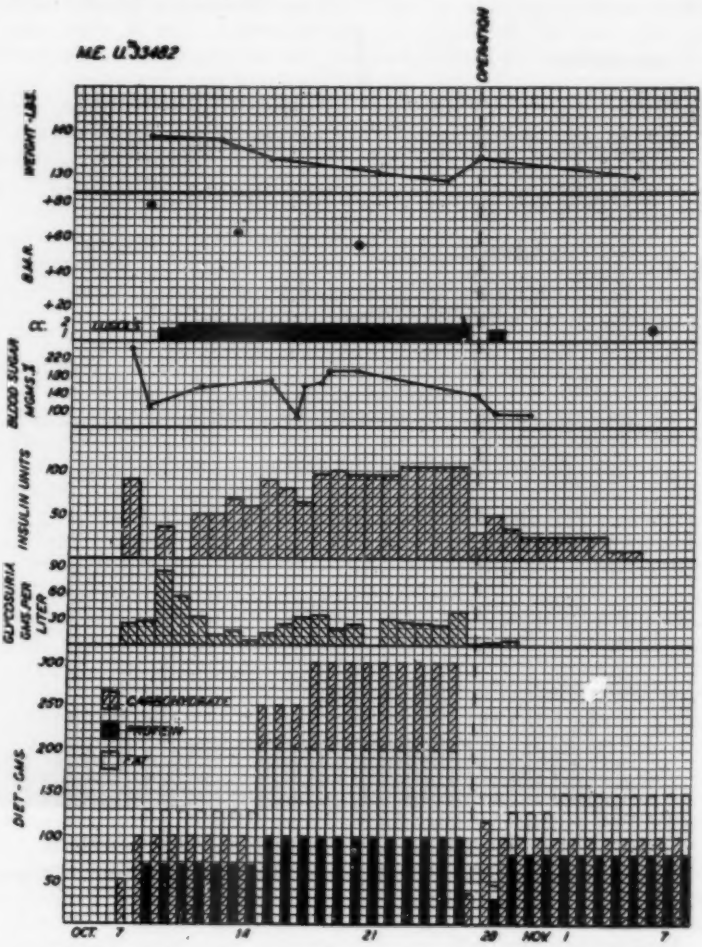

CHART II. DEFICTING THE CLINICAL COURSE OF PATIENT M. E.

Urine: Clear, straw-colored, acid, Sp. Gr. 1.015, Albumin, trace. Sugar 1.3 per cent. Microscopic: few W.B.C. Acetone +.

Blood: R.B.C. 4,720,000. Hbg. 90 per cent, W.B.C. 6550.

Blood Wassermann: Negative.

Blood chemistry: Sugar 240 mg. per cent, CO_2 combining power 46.6 vols. per cent.

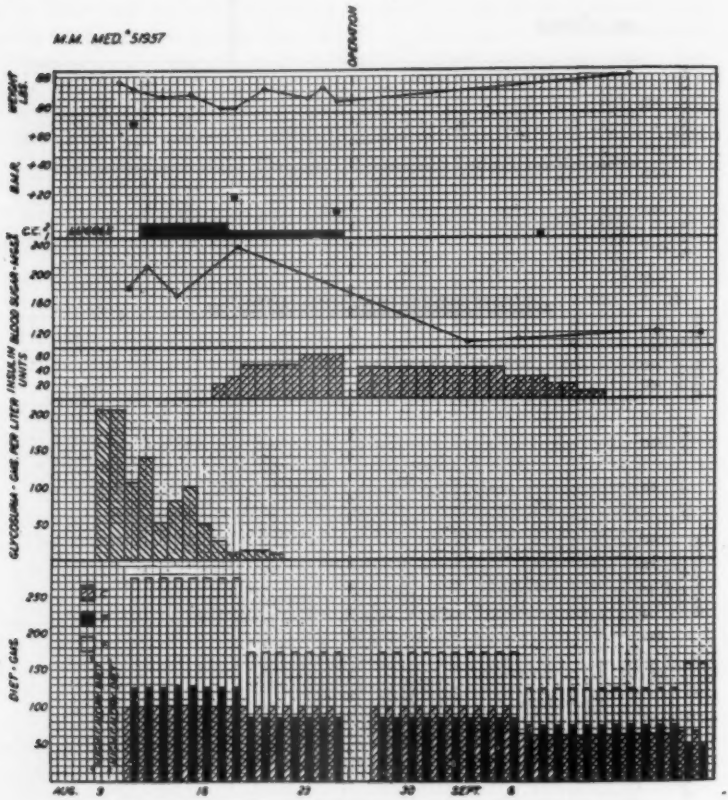

CHART III. SHOWING THE CLINICAL COURSE OF PATIENT M. M.

Approximate composition of "high calory" diet in this instance: P. 150 gms., C. 300 gms., F. 250 gms.

Basal metabolic rate: +77.

Diagnosis: Diabetes mellitus, adenoma of the thyroid, hyperthyroidism, Horner's syndrome.

The patient's course in the hospital is depicted in Chart II. During the first

day she received 50 gm. carbohydrate and 90 units of insulin. For seven days thereafter she received 1850 calories including approximately 150 gm. available glucose. *Acetonuria persisted until Oct. 15th* when she was given a diet of 2300 calories with 320 gm. available glucose. This was subsequently raised to 3400 calories with 380 gm. available glucose. Glycosuria persisted throughout the preoperative course despite the daily administration of 80–100 units of insulin. Lugol's solution was given from Oct. 9th to Oct. 25th. The basal metabolic rate fell gradually.

On Oct. 27th Dr. Penick performed a sub-total thyroidectomy. There was a moderately severe reaction characterized by fever (to 102°F.) and tachycardia (to 150), beginning 24 hours after operation and subsiding within 48 hours.

During convalescence the patient received about 2100 calories daily, containing approximately 160 gm. available glucose. Glycosuria abated rapidly. The dosage of insulin was gradually reduced; the patient required none at the time of her discharge.

Case II. M. M. (Med. no. 51957), a white woman, aged 25, was admitted to the medical service, Johns Hopkins Hospital, August 9, 1924, complaining of goiter and diabetes. As a child and during adolescence she had enjoyed good health except for occasional attacks of sore throat.

Present illness: Five years prior to admission the patient had suffered from a "nervous spell" of a year's duration characterized by nervousness, emotional instability, loss of weight despite increased appetite, and fatigability. Improvement coincided with her last (second) pregnancy and for one year she was relatively free from symptoms. Three years before entering the hospital she noted palpitation, nervousness, dyspnoea on exertion and loss of weight; no polydypsia or polyuria described at that time. During the next year the patient noted enlargement of her neck. During the last four months prior to admission her appetite became ravenous and she drank large quantities of water. This was accompanied by polyuria, diarrhoea, sweating and tremor. Menses ceased in May, 1924. Sugar was first demonstrated in the urine during April 1924. Weight—Best (1919) 150 lbs. On admission 80 lbs.

Physical examination: Temperature 98.4°F., Pulse 140, Respirations 30. The patient was a decidedly undernourished young woman, nervous and irritable. Skin flushed, moist and warm. Pronounced exophthalmos with lid-lag, and difficulty of convergence. Thyroid moderately and diffusely enlarged; well marked thrill and bruit over the upper poles. Heart normal; beat active and forceful, sounds clear and rapid; soft systolic murmur in the pulmonic area. B. P. 135/70. Lungs clear. Abdominal organs showed no abnormalities.

Urine: Clear yellow. Sp. Gr. 1.030 Acid. Sugar ++++, Albuminuria 0. Acetone +++, Microscopic: few W.B.C.

Blood: R.B.C. 4,368,000. Hbg. 78 per cent, W. B. C. 7,100.

Blood chemistry: N.P.N. 28 mg. per cent. Sugar 205 mg. per cent.

CO_2 combining power: 47.5 vols. per cent.

Basal metabolic rate: +66.

Diagnosis: Hyperthyroidism, diabetes mellitus.

The clinical course of this case is shown in Chart III. During her first two days in the hospital the patient received a "high calorie" diet composed approximately as follows: Protein 150 gm. Carbohydrate 300 gm. Fat 250 gm.; 200 gm. glucose were excreted daily. Lugol therapy was begun Aug. 11th, and a 3300 calorie diet was prescribed containing approximately 200 gm. available glucose. The patient's tolerance for carbohydrate increased rapidly but the blood sugar remained high and glycosuria persisted until insulin treatment was begun Aug. 16th and the carbohydrate intake was subsequently decreased. The basal metabolic rate fell steadily, and the patient showed decided symptomatic improvement. On August 26th a double partial lobectomy was performed by Dr. Rienhoff. There was only a slight postoperative reaction with no reappearance of glycosuria. Insulin was continued for ten days after operation at 45 units per day. It was then reduced gradually until at the time of the patient's discharge Sept. 19th it had been entirely withdrawn. The patient was then able to take 1900 calories with 100 gm. available glucose without having glycosuria.

During the next three weeks she remained at home. She observed no particular precautions with regard to her diet. She returned for observation and was readmitted to the hospital Oct. 7th, 1924. At that time the blood sugar was 245 mg. per cent, basal metabolic rate −7. She subsequently developed a psychosis which made necessary her transfer to the psychiatric service and later to a sanitarium where she died April 21, 1926.

Judging from the patients' accounts, in the case of M. E. hyperthyroidism apparently had complicated diabetes; in that of M. M. diabetes seemed to have developed following hyperthyroidism. At the time of their admission to the hospital it was impossible to say which abnormality had occurred first. But in both instances the carbohydrate tolerance improved as the symptoms and signs of hyperthyroidism abated under appropriate treatment.

Hyperglycaemia and glycosuria have been noted as characteristic of many cases of hyperthyroidism[1] since the observation of Tachau (26). The ingestion of 100 gm. glucose is often followed, in such instances, by glycosuria; the blood-sugar curve may rise to an abnormally high level and fall more slowly than normal. Certain authors, among them Lorand (18), Holst (13), and John (14), have ascribed these abnormalities of carbohydrate metabolism to the specific effect of hyperthyroidism upon the islet tissue of the pancreas, and have

[1] Extensive reviews of the literature have been published by John (14), by Wilder (27) and by Ginsberg (9).

maintained that hyperthyroidism may play a rôle in the genesis of diabetes. However, not only does this assumption lack histological proof but it also fails to explain the fact that, despite the presence of hyperglycaemia the *utilization* of carbohydrate is increased by the administration of thyroxin or during clinical hyperthyroidism. Thus Ambrus (2) demonstrated abnormally high glucose consumption by the hearts of thyroxinized animals. Du Bois (8) observed that, in patients with exophthalmic goiter and high basal metabolic rates, the respiratory quotient reacted in the normal fashion, being low (0.77) after a prolonged fast, but rising to a high value (0.94 to 0.98) following the ingestion of 100 gm. glucose. In one instance the subject derived 89 per cent of his total caloric requirement from carbohydrate under these circumstances. Sanger and Hun (24) made a similar study and, in addition, followed the development and subsidence of hyperglycaemia. These authors confirmed the observation that available glucose was utilized in large amounts in cases of hyperthyroidism.

Thyroid feeding, or the administration of thyroxin to animals, leads to depletion or exhaustion of the glycogen deposits in the liver and muscle (6, 7, 11, 17). Such increase of glycogenolysis results in hyperglycaemia so long as adequate amounts of glycogen remain. Moreover, the hyperglycaemic action of adrenalin is strikingly enhanced in animals which have received thyroid extract (6). Following prolonged administration of thyroid extract (6), or in the course of severe hyperthyroidism in man (12), the exhaustion of glycogen reserves may result in hypoglycaemia.

It appears, therefore, that the metabolism of carbohydrate in the presence of hyperthyroidism is at fault less in the ability of the organism to store carbohydrate than in the abnormally rapid break-down of glycogen. There is considerable evidence that, in hyperthyroidism (5, 16, 20), particularly during exercise, glycolysis proceeds to the formation of lactic acid in quantities greater than normal. Indeed, it has been suggested (10) that the cause of the increased oxygen consumption characteristic of this condition is to be sought, in part at least, in the demand occasioned by increased anaërobic glycolysis.

On the other hand, observations upon the respiratory quotient both in human diabetics (1, 21, 22) and in the isolated tissues of depancreatized animals (23) indicate that little or no carbohydrate is metabolized.

In this condition the ingestion of carbohydrate is followed by hyperglycaemia and glycosuria of greater or lesser degree dependent upon the severity of the diabetes or upon the dosage of insulin (see chart I).

It should be noted, however, that Soskin (25) reports normal respiratory quotients in depancreatized dogs, which had received insulin during convalescence from the operation but received none during the period of observation. Even while his animals excreted large amounts of glucose in the urine their respiratory quotients indicated that carbohydrate was utilized. As a result of these and similar observations Soskin subscribes to the theory that the hyperglycaemia and glycosuria of diabetes is the result of excessive formation of glucose from fat. MacLeod (19) has made a similar suggestion.

Whichever explanation be accepted, the fact remains that carbohydrate administered to a diabetic in excess of his tolerance appears in the urine as glucose (See Chart I, W. A.). The patient with exophthalmic goiter (Chart I, G. L. B.), on the other hand, even though sugar appear in the urine, utilizes more carbohydrate the more he receives, unless diabetes and hyperthyroidism coexist. In the normal individual, under the action of insulin, glucose disappears from the circulating blood; a portion of this is stored as glycogen, the remainder is disposed of through some reaction involving the use of oxygen (3, 4). If sufficient insulin is administered hypoglycaemia results; secondarily to this, glycogen is broken down, chiefly in the liver, and glucose is discharged into the blood. Burn and Marks (6) have demonstrated that this secondary reaction may be eliminated by section of the nerves to the liver, by removal of the adrenals, or by thyroidectomy.

Thyroxin is therefore antagonistic to insulin in that (1) it itself promotes glycolysis in the tissues and (2) as long as the glycogen in the liver is not exhausted, it enhances the glycogenolytic action of adrenalin.

The diabetic patient, then, who develops hyperthyroidism, suffers a complication which creates abnormal demands upon his already inefficient carbohydrate metabolism, both by virtue of an elevation of basal metabolism and by enhancement of glycogenolysis. A mild case of diabetes may thus be increased in severity or, in a more severe case, acidosis and coma may be precipitated.

Experience has shown that the majority of such cases do well after

subtotal thyroidectomy. Therapeutic measures should first be directed toward the relief of the hyperthyroidism preparatory to operation. To this end the patient should be kept at rest; he should receive a diet well in excess of his caloric requirements, and Lugol's solution in adequate quantities. His lowered tolerance for carbohydrate may be reinforced by the administration of sufficient insulin to control the metabolism of the large amounts of carbohydrate contained in the diet. It is not always possible under these conditions to cause the glycosuria to disappear completely; every effort should be made, however, to keep the urine acetone-free. Following operation the patient's tolerance for carbohydrate may be determined and his diet regulated or insulin prescribed accordingly.

SUMMARY

1. The clinical courses of two patients are described, in which diabetes mellitus and hyperthyroidism coexisted.

2. The carbohydrate metabolism in hyperthyroidism is contrasted with that in diabetes mellitus. In the presence of hyperthyroidism this is at fault less as regards the ability of the organism to store carbohydrate than in the abnormally rapid breakdown of glycogen. The diabetic patient, on the other hand, suffers from a limited carbohydrate tolerance; carbohydrate administered in excess of this appears in the urine as glucose. Hyperthyroidism superimposed upon diabetes mellitus creates abnormal demands upon an already inefficient carbohydrate metabolism: (a) by augmenting the basal metabolic rate, and (b) by enhancing glycogenolysis.

The author desires to acknowledge the assistance of Miss Rebecca Marshall in the preparation of the charts.

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PROGRAMS AND LECTURES, 1931–1932

Programs of The Johns Hopkins Medical Society

October 12, 1931

1. A Study of the Late Effects of the Toxemias of Pregnancy. C. H. Peckham.
2. Some Effects of Thyroxine Upon Cardiac and Skeletal Muscle. E. C. Andrus and Donald McEachern.

November 9, 1931

1. Studies on Adrenal Cortical Hormone with Presentation of Cases. G. A. Harrop, Jr., A. Weinstein and A. Marlowe.
2. A Review of 950 Cases of Carcinoma of the Breast Operated on in the Johns Hopkins Hospital, 1889–1931. Wm. Francis Rienhoff, Jr.

December 14, 1931

1. Pneumonia from the Aspiration of Fats. T. C. Goodwin.

Abstract. A review of the recent literature on lipoid cell pneumonia reveals the following important point; the oil placed in the nose or mouth can find its way to the lung, and may carry infection with it. The amount of reaction in the lung is proportional to the amount of free fatty acid in the oil aspirated. In general, therefore, animal oils are the most injurious, mineral oil next, and vegetable oils least. The pathological picture is briefly described.

Since 1924, there have been 21 cases of lipoid cell pneumonia, in the autopsy records of the Johns Hopkins Hospital. One of the cases occurring during the last 18 months was diagnosed clinically. (This case is reported in detail.) Of the 21 cases, 13 were in infants below the age of two years and three were in adults. In the infants there is usually the history of a combination of illness, cough and the use of some kind of oil in the nose or mouth. In a few cases, the aspiration of vomitus was the only clear etiological factor. For 14 cases including those of all the older children and adults, there had been some neurological condition favoring aspiration (convulsions, pharyngeal paralysis, coma, etc.).

The clinical diagnosis of uncomplicated lipoid cell pneumonia can be made on the following points: (1) history of the use of fats or oils in the nose or mouth. (2) Persistance of pulmonary consolidation, usually central and posterior, gradually becoming less over a long period of time. (3) X-ray change showing more consolidation than physical signs would indicate. (4) Absence of or very low-grade fever. (5) Normal white count. (6) Absence of pleural reaction. The rarity with which the uncomplicated condition occurs makes the diagnosis difficult.

Care is advised in the nasal or oral use of oil in very weak or unconscious patients. Substitution of the more bland olive, poppy or sesame oils in place of animal fats and mineral oils is suggested. Lipoid cell pneumonia should be considered in the diagnosis of a chronic pulmonary consolidation.

2. The Influence of Copper on Iron Metabolism. H. W. JOSEPHS.
3. Dietary Phosphorus and Parathyroid Tetany. D. H. SHELLING.

Abstract. In an attempt to study the calcium and phosphorus balance in parathyroidectomized rats difficulty was encountered in inducing the operated animals to eat certain diets. Whereas they ate the stock diet in usual amounts, they refused diets which were either low in calcium but optimal in phosphorus or optimal in calcium but excessive in phosphorus. Previously it had been observed that the symptoms of tetany paralleled closely loss of weight, and apparently, the loss of weight was due to an anorexia. This suggested that the excess of phosphorus over calcium in the diet was responsible for the anorexia and the tetanic symptoms.

The experiments were repeated and the quantitative food intake was measured daily. It was found, as originally observed, that parathyroidectomized rats eat diets containing either optimal amounts of calcium and phosphorus or those having large amounts of calcium and optimal or low phosphorus, but refuse rations which are either low in calcium and optimal in phosphorus or optimal in calcium but excessive in phosphorus. The diet most efficacious in relieving tetany and in raising the serum calcium levels was one in which the phosphorus was low.

That the anorexia was due to the dietary phosphorus was evident from the fact that it was present only when the dietary phosphorus was in the form which could be utilized by the animal organism but absent when the phosphorus salts could not be utilized. Sodium metaphosphate and hypophosphite belong to the latter group.

Metabolism experiments indicated that, unlike unoperated rats, parathyroidectomized animals tended to excrete their excess phosphorus through the bowel as the insoluble salt. If the diet contained an insufficient amount of cations capable of forming insoluble salts with phosphorus, the excess phosphorus remained in the body although an attempt was made to excrete it through the kidney. The retained phosphorus in the blood prevented the solubility of what little calcium was ingested, and tetany ensued. Apparently, the anorexia in rats and vomiting in dogs are protective mechanisms to avoid diets conducive to tetany. During the tetanic periods the amounts of phosphorus in the urine were fairly abundant but as soon as an adequate amount of calcium was added to the diet, the path of phosphorus excretion shifted to the feces and the phosphorus in the urine diminished or disappeared entirely.

Magnesium relieved tetany by inactivating the circulating phosphorus and also by removing the excess phosphorus into the bowel. Strontium behaved like calcium in this respect.

In a patient with parathyroid tetany, in whom the blood inorganic phosphorus remained fairly high, it was difficult to raise the serum calcium above tetanic levels although calcium (2.0 gm.) was given daily. When the dietary phosphorus was diminished to one fourth of the original amount and the calcium kept at the same level, the serum inorganic phosphorus fell, the calcium rose and tetany disappeared. Oral administration of magnesium carbonate had a similar effect. The urinary phosphorus excretion resembled that described for the rats, *i.e.*, when tetany was manifest, the urine contained phosphorus but it disappeared with the lowering of the phosphorus content of the diet and with the relief of tetany.

4. Studies in Fat Metabolism in Infancy. L. E. HOLT, JR.

Abstract. Metabolism studies have been carried in a series of normal infants in an attempt to evaluate the factors responsible for differences in fat absorption. It was found that the size of the fat globules was without influence on the absorption of fat. Retention was quite as satisfactory when butter was fed by spoon, as in experiments in which cow's milk or homogenized cow's milk was used.

In order to find out whether the somewhat lower fat retention on cow's milk as compared with breast milk was due to differences in mineral content or to differences in the fat itself, these factors were varied independently. The effect of mineral was evaluated by employing cow's milk fat incorporated in (1) skimmed breast milk, (2) skimmed cow's milk and (3) skimmed cow's milk to which additional mineral had been added, approximately doubling the quantity. The following retention figures represent averages for such experiments:

Cow's milk fat + skimmed breast milk..... 95.5 per cent retained
Cow's milk fat + skimmed cow's milk..... 86.7 per cent retained
Cow's milk fat + double ash skimmed cow's milk..... 81.4 per cent retained

Apparently the chief reason for the lower retention of fat on cow's milk as compared with breast milk is the higher ash content of the latter.

However, differences in retention were observed when the only factor varied was the fat itself. In a series of experiments in which skimmed cow's milk was used as a basal diet and various fats added to this, the following retention figures were obtained:

FAT FED	IODINE VALUE	AVERAGE RETENTION
		per cent
Corn oil and olive oil	90–120	92.8
Breast milk fat	56	89.9
Cow's milk fat	26	86.7
Tripalmitin + Tristearin	2	61.4

It would thus appear that more highly unsaturated fats are better absorbed than saturated fats.

By determinations of the iodine value and thiocyanogen value of the food fat and fecal fat, we have been able to calculate the retention of the various fractions in any mixed fat. Evidence has been obtained which suggests that, when fat mixtures are fed, there is a selective absorption of unsaturated fats.

January 11, 1932

1. Intracisternal Treatment of Optic Atrophy. Demonstration of a Case. P. F. METILDI.

Abstract. The case presented was that of a forty-two year old white man who developed an extra-genital chancre in 1914, but was insufficiently treated. In 1917 he was admitted to the Johns Hopkins Hospital complaining of dimness of vision in the left eye and other symptoms suggestive of syphilis of the central nervous system. The physical and serological findings were those of tabo-paresis and primary optic atrophy of the left eye. He was inoculated with malaria in 1917, from which he recovered without complica-

tions. During the years 1928–29–30 he received antisyphilitic treatment (neo-arsphenamine and bismuth). All his symptoms disappeared with the exception of the diminished visual acuity and constriction of the visual field in the left eye for both form and color. In 1931 he received 12 intracisternal injections of neo-arsphenaminized homologous serum at intervals of two weeks. At the end of the course he had improved subjectively and objectively. The visual field showed a very definite increase in size for both form and color, and the visual acuity which had been 20/100 ever since the original examination was 20/70 at the end of the course. The patient at present is asymptomatic and on probation.

2. Occult Syphilis, A Neglected Factor in Diagnosis and Treatment. U. J. WILE, University of Michigan.

February 29, 1932

The Syndrome of Pituitary Basophilism. PROF. HARVEY CUSHING, Harvard Medical School.

March 14, 1932

Investigations on the Underlying Causes of Deafness. S. J. CROWE.
Discussion opened by William H. Howell.

April 18, 1932

The Rôle of the Posterior Pituitary Secretions in Metabolism. E. M. K. GEILING and A. M. DELAWDER.
Human Bodies and Human Beings. T. WINGATE TODD, Western Reserve University.

May 9, 1932

Pathological Calcification. DAVID BARR, Washington University.
Election of Officers.

PROGRAMS OF THE JOHNS HOPKINS MEDICAL HISTORICAL CLUB

October 26, 1931

1. History of the Surgical Clinic. DEAN LEWIS.
2. The Institute for the History of Medicine at the University of Leipzig. HENRY E. SIGERIST, Leipzig Institute.

December 21, 1931

1. The History of Laryngology and Rhinology and the Influence of America on this Specialty. JOSEPH H. BRYAN, Washington, D. C.
2. Edwin James, Surgeon, Botanist, Explorer. IRVING S. CUTTER, Northwestern University Medical School.

February 15, 1932

1. The Children of Robert and Clara Schumann: A Study in Family History. FIELDING H. GARRISON.
2. Medicine in Soviet Russia. LEWELLYS F. BARKER.

May 9, 1932

1. Witchcraft. CHRISTIAN DEETJEN.
2. John Bruce MacCallum. ARCHIBALD MALLOCH, New York Academy of Medicine.

PROGRAMS OF THE JOHNS HOPKINS MEDICAL RESEARCH SOCIETY 1931–1932

October 30, 1931

Factors Influencing the Absorption of Fats. L. E. HOLT.

November 20, 1931

Studies on the Mode of Action of Thyroxin on the Heart. E. C. ANDRUS.
Experiments on the Question Whether Yaws Confers Immunity to Syphilis. T. B. TURNER.

January 15, 1932

Further Studies on Parathyroid Physiology. READ ELLSWORTH.
A Hitherto Undescribed Enzyme Secreted by the Stomach. LAY MARTIN.

February 12, 1932

Effect of Magnesium on Calcium and Phosphorus Metabolism. LASLO KADJI.
A Contribution to the Pathogenesis of Retinitis Pigmentosa. JONAS FRIEDENWALD and EUGENE CHAN.
Syphilitic Nephritis (Congenital and Acquired). ARNOLD R. RICH.

March 18, 1932

Serological Reactions in Acute Bacterial Infections. W. S. TILLETT.
Researches on Cardiac Puncture in Human Beings. ARTHUR GROLLMAN.

April 22, 1932

Studies on Adrenal Cortical Function. G. A. HARROP and F. B. KINDELL.
A Study of the Protective Action of Antibody in Immunized Animals Deprived of Leucocytes. A. R. RICH and MISS CLARA MCKEE.

May 13, 1932

The Rôle Played by the Endocrine Glands in the Production of Gross Bodily Activity. CURT RICHTER.

The Comparison of the Effect of Pituitary Secretion (Pitressin) with that of Cyanide. E. M. K. GEILING.

The Johns Hopkins Medical Research Society records the death of Dr. Frederic B. Jennings, Jr., with a sense of great loss. Dr. Jennings was a valued member of the Society. He contributed much to its success both by the high character of his own work and by his sound and clear-sighted criticism. Through his death the members of the Society have lost a stimulating fellow-worker and friend.

LECTURES UNDER THE AUSPICES OF THE HERTER LECTURE FOUNDATION

BY DR. MAJOR GREENWOOD, F.R.S., Professor of Vital Statistics in the School of Hygiene and Tropical Medicine, of London University

December 2, 1931

1. History of the Development of Epidemiology. The Study of Disease as a Mass Phenomenon.

December 3, 1931

2. The Experimental Method in Epidemiology. The Relation of Immigration to the Persistence of an Infection in a Community.

December 4, 1931

3. Pre-immunisation as a Weapon of the Sanitarian. Natural and Acquired Immunity.

Lectures by PROFESSOR HENRY E. SIGERIST, M.D., Professor of the History of Medicine and Director of the Institute of the History of Medicine of the University of Leipzig, Visiting Lecturer in the Institute of the History of Medicine, Johns Hopkins University

October 15, 1931

1. Primitive Conceptions of Disease.

October 22, 1931

2. The Religious Character of Oriental Medicine.

October 29, 1931

3. The Philosophical Attitude of the Greek Physicians toward Medicine.

November 5, 1931

4. The Dawn of Modern Medicine.

November 12, 1931

5. The Cultural Background of Modern Medicine.

November 19, 1931

6. The development of Medicine During the Nineteenth Century.

THE WILLIAM SYDNEY THAYER AND SUSAN READ THAYER LECTURES IN CLINICAL MEDICINE

By A. R. DOCHEZ, M.D., Professor of Medicine, Columbia University College of Physicians and Surgeons, New York

March 22, 1932 and March 23, 1932

A Limited Consideration of Certain Aspects of Acute Infection of the Respiratory Tract.

THE CHARLES E. DOHME MEMORIAL LECTURES

By ERNST WALDSCHMIDT-LEITZ, Ph.D., Professor of Chemistry and Director of the Institute of Biochemistry, Deutsche Technische Hochschule, Prague, Czechoslovakia

April 20, 1932

1. On the Specificity and Mode of Action of Proteolytic Enzymes.

April 21, 1932

2. The Structure of Proteins.

April 22, 1932

3. On the Biological Significance of Enzymatic Activation.

THE LAENNEC SOCIETY

Program to Commemorate the Fiftieth Anniversary of the Discovery of the Tubercle Bacillus

April 11, 1932

Display of Koch's Original Communication. HENRY BARTON JACOBS.
Robert Koch and His Discovery of the Tubercle Bacillus. WILLIAM H. WELCH.
The Influence of the Discovery on Sanatorium Treatment. LAWRASON BROWN, Saranac, New York.

The Organized Crusade Against Tuberculosis. KENDALL EMERSON, Director, National Tuberculosis Association.

Results in the Control of Tuberculosis. LOUIS I. DUBLIN, Vice-President Metropolitan Life Insurance Company.

The Development of the Pathology of Tuberculosis following the Discovery of the Tubercle Bacillus. ARNOLD RICE RICH.

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